Coagulation in Liver Disease

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Vijay Vohra

13.1 Introduction

The liver plays an important role in coagulation pathways which is involved in primary and secondary tertiary haemostasis. It is the site of production for most of the coagulation factors except for von Willebrand factor (vWf) which is synthetised by the vascular endothelium. The liver also produces anticoagulant factors—Anti-thrombin III, Protein C and Protein S. Patients with advanced liver disease are associated with impairment of coagulation. Normally there is a balance between procoagulant and anticoagulant system which can be disturbed during progression of liver disease. As the liver disease advances multiple changes occur in the haemostatic system, thereby leading to reduced level of both procoagulative and anticoagulative factors—which were being synthetised by the hepatocytes and sinusoidal cells. In addition to this there could be deficiency of vitamin K which leads to abnormal clotting factor production as this vitamin (vitamin K) is required for gamma carboxylation. So the coagulation factors produced by the liver, which is already damaged, produce clotting factors which may be abnormal in nature. In End Stage Liver Disease (ESLD) there is also reduced capacity to clear the activated clotting factors and their inhibitor complexes from the circulation. So the overall effect of the liver disease is quite complex and can lead to bleeding as well as thrombotic complications. As the disease progresses it leads to development of portal hypertension which results in splenomegaly and thrombocytopenia. Thrombocytopenia can further be accentuated due to decreased synthesis of thrombopoietin in the failing liver.

13.2 Haemostasis in Health

Haemostasis is a physiological process whereby coagulation is initiated when there is a breach in the integrity of the vessel wall leading to clot formation and minimizing bleeding. This is followed by appropriately timed lysis of this clot and restoring normal circulation. The coagulation and clot dissolution are inter-linked and are regulated in a precise manner with their own inhibitors being activated in the process. The outcome of this finally balanced process may result in bleeding or thrombosis.

The haemostatic balance is dependent on a very complex interaction between pro- and anticoagulants as well as the effect of fibrinolytic proteins. The process of coagulation starts when tissue factor is exposed on sustaining injury to the vessel wall. This leads to activation of Factor VIIa which further activates Factor X–Xa.

V. Vohra (✉)
Liver Transplant, GI Anesthesia & Intensive Care, Medanta the Medicity, Gurgaon, India
e-mail: vijay.vohra@medanta.org

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Thrombin is generated by the effect of Factor Xa on prothrombin (Factor II). Protein C, S and antithrombin have an inhibitory effect on thrombin generation (Fig. 13.1).

Thrombomodulin also plays an important part in haemostasis. This glycoprotein is present on the endothelial surface and acts as an anticoagulant by activating protein C. Activated protein C has an inhibitory effect on thrombin [1].

There are complex enzymatic reactions taking place simultaneously through the tissue factor pathway (extrinsic pathway) as well as intrinsic pathway (contact activation pathway). Besides other factors involved, fibrinogen and platelets are two very important ingredients required to repair the damage to the injured vessel wall.

Standard laboratory tests of coagulation—Prothrombin Time (PT) or International Normalized Ratio (INR) and Activated Partial Thromboplastin Time (APTT)—guide the management of patients with deranged coagulation. There are many limitations to these tests including a long turnaround time when prompt treatment of bleeding is required. A ratio of 1.5 times the normal of PT/APTT is considered abnormal and may warrant correction depending on the clinical status. PT primarily gives information about intrinsic pathway whereas APTT is influenced by the processes involved in the intrinsic pathway (Fig. 13.2).

Information received from PT or APTT is generally used for assessing bleeding risk or when an invasive procedure/surgery is to be performed. It should be kept in mind that PT and APTT are plasma-based coagulation tests and they were initially designed to monitor treatment with vitamin K antagonists and heparin therapy. These tests therefore have limited value in assessing peri-operative bleeding risk. Another whole blood coagulation test Viscoelastic Test probably would give better information on management of bleeding patients and guiding therapy on the basis of abnormalities seen on thromboelastography (TEG).

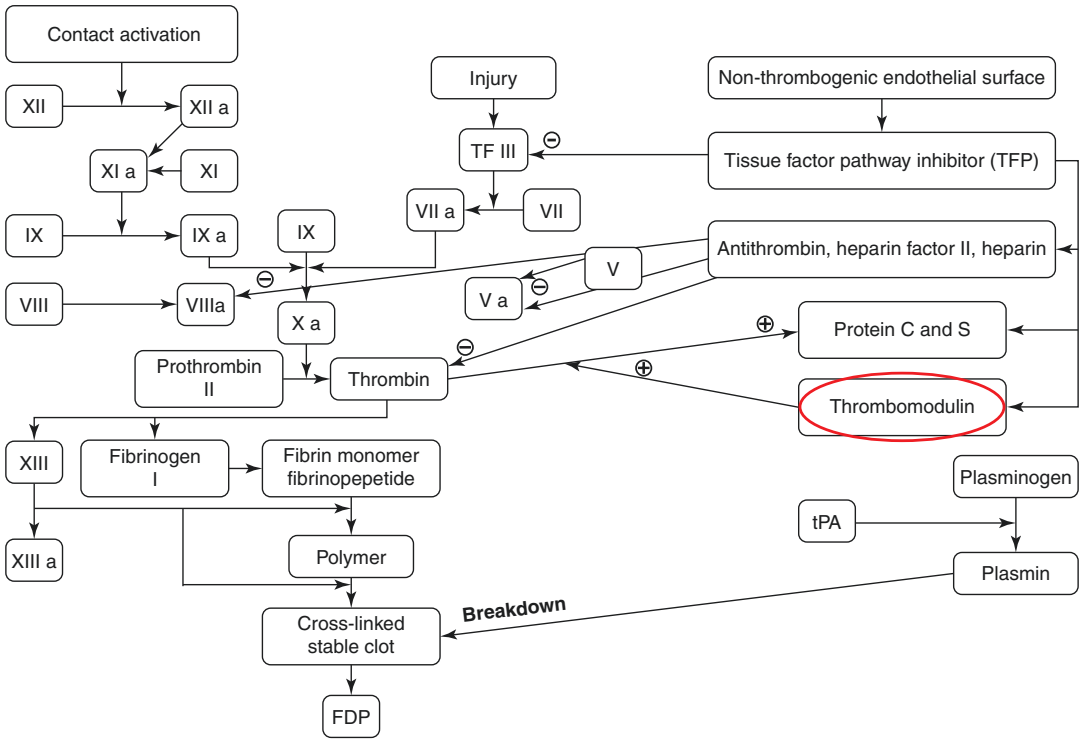


Fig. 13.1 pathways

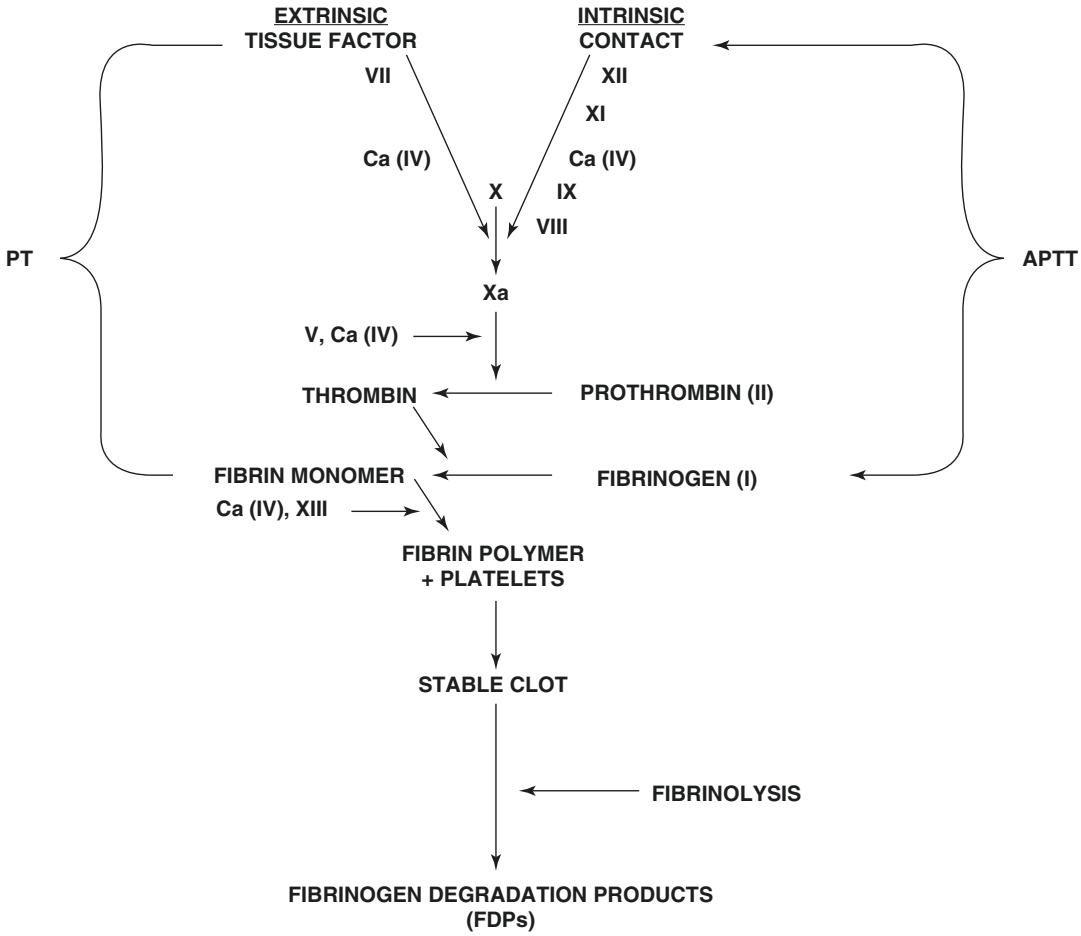


Fig. 13.2 Coagulation and conventional testing. PT—extrinsic pathway primarily, APTT—intrinsic pathway mainly

13.3 Coagulation in Chronic Liver Disease

The haemostatic system in liver disease patients affects the initial clot formation, secondary clot formation as well as tertiary haemostasis. All three phases of coagulation are altered in liver disease patients to a varying degree, disease aetiology playing an important role.

In primary haemostasis, the vessel wall injury results in exposure of platelet adhesion protein to the platelets which results in the formation of a platelet plug. Release of tissue factor leads to activation of coagulation cascade in the plasma and quickly results in the formation of a fibrin mesh. In chronic liver disease there is thrombocytopenia due to various reasons which can alter the primary haemostasis—platelet plug formation. To counter this there is high level of vWf. The elevated levels of vWf are as a result of endothelial activation. Activity of vWf is enhanced further because of reduced clearance by the cirrhotic liver as well as increased synthesis in the liver.

As the coagulation cascade gets activated during secondary haemostasis, complex reactions involving both pro- and anti-haemostatic proteins come into play (Fig. 13.1) [2].

The coagulation factors II, V, VII, IX and XI are reduced in patients with chronic liver disease but on the other hand factor VIII levels are often elevated [3]. This is due to increased synthesis from extrahepatic sites such as spleen, kidney and lung [4]. Factor VIII activity is further

enhanced due to increased level of vWf which is the carrier protein for factor VIII. The clearance of activated factor VIII is also reduced in the failing liver. Counting the decreased production of procoagulant factors, there is decreased production of anticoagulants like protein C, protein S, anti-thrombin and heparin co-factor II—all being produced in the liver. As a result there is a fine balance of pro- and anticoagulant proteins which are very much lower than the levels seen in healthy individual.

After the bleeding which stops on formation of a fibrin clot, there is dissolution of this fibrin clot—fibrinolysis (Fig. 13.2). The fibrinolytic system is again balanced by pro- and anti-fibrinolytic proteins. There are low levels of plasminogen and high levels of Plasminogen Activator Inhibitor 1 (PAI-1) which prevent fibrinolysis whereas high levels of Tissue Plasminogen Activator (t-PA) and low levels of factor XIII facilitate fibrinolysis. Exaggerated hyperfibrinolysis is quite often seen during liver transplantation during anhepatic phase as the clearance of t-PA is hampered.

Coagulation disorders produced in chronic liver disease may require correction if there is a gross deterioration in prothrombin time or before doing any invasive procedures. Non-bleeder with abnormal clotting studies may not require any correction during the normal course of management. The standard screening tests for assessing clotting status may not depict any abnormality till the procoagulant levels are reduced by 60–70% of the normal values [5]. There is no utility of measuring individual clotting factor concentrations in the normal course of the disease except in acute liver failure where factor V levels less than 20%/30% indicate need for liver transplantation (Clichy Criteria). This is relevant only if you have a practice to list your patients for transplantation on the basis of Clichy Criteria instead of the more universally used King's College Hospital (KCH) criteria.

13.4 Coagulation in Acute Liver Failure

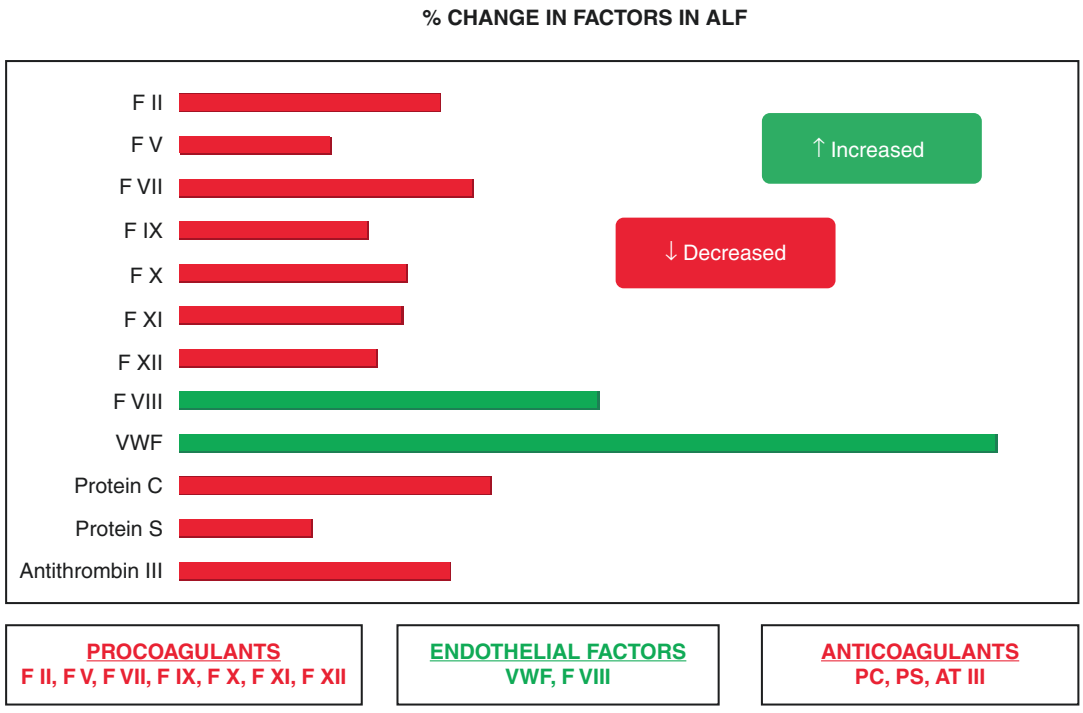
In candidates for transplantation in Acute Liver Failure (ALF), there is gross derangement of prothrombin time but this is not replicated in the viscoelastic tests—TEG in up to 35% patients shows a hypercoagulable graph. This can be explained by the reduction in both procoagulant and anticoagulant factors along with increase in vWF and factor VIII in circulation (Fig. 13.3) [6].

In acute liver failure there is no evidence of prophylactic use of blood products to correct the abnormal coagulation profile though PT can be grossly deranged.

Thrombin generation in ALF is near normal after initial thrombin formation with activation of factor VIII, IX and XI. The rapid production of thrombin is facilitated by the availability of increased level of factor VIII. This process is further enhanced by reduced thrombin inactivation due to activated protein C resistance.

The platelet size in ALF is increased which is evident by the increase in the mean platelet volume, although the platelet count may even be reduced. This viewpoint is supported by the fact that in majority of the patients with ALF, TEG shows a hypercoagulable pattern. Platelet and fibrinogen contribute equally to the clot strength in healthy individuals whereas in ALF platelets can contribute up to 75% of clot strength [6, 7]. This shows there could be disproportionate functional hypofibrinogenemia.

The belief that increasing bleeding tendency in ALF as shown by traditional clotting test is not borne out by the assessment of clot using TEG and thrombin generation test.



Adapted from Reference No. 6

Fig. 13.3 Percentage change in factors in ALF. (Adapted from Agarwal B, Wright G, Gatt A, Riddell A, Vemala V and Mallett S et al. Evaluation of coagulation abnormalities in acute liver failure. Journal of Hepatology 2012;57(4):780–786)

13.5 Procoagulant Factors

The liver is the site of production of majority of the procoagulant factors—Factors II, V, VII, VIII, IX, X, XI, XII and XIII besides producing anticoagulant factors as well. As the synthetic function of the liver deteriorates, there is marked decline in the production of coagulation factors. However one procoagulant factor which is increased is factor VIII—This is produced mainly by the sinusoidal cells of the liver with minor contribution from the spleen, endothelial cells and the lung (Table 13.1).

Majority of the procoagulant factors are vitamin K dependant, which is deficient in chronic liver disease. Vitamin K deficiency could be because of reduction in the dietary intake, inadequate absorption due to bile acids, diminished storage and decreased production in the intestines. Treatment with antibiotics can also destroy the intestinal bacteria that syntheses vitamin K [8]. There are instances in end-stage liver disease when there are high levels of clotting factors in the presence of near-normal vitamin K—primary biliary cirrhosis and primary sclerosing cholangitis are examples of such states. This can even result in hypercoagulable states as seen in viscoelastic testing with decreased reaction time (r time), increased alpha angle and maximum Amplitude (mA) on TEG.

Table 13.1 Sites of synthesis of clotting factors

Factors	Synthesis	Half-life (h)
Factor I or fibrinogen	Liver, extrahepatic sites	72–120
Factor II or prothrombin	Liver	72
Factor V (labile)	Liver, endothelium, platelets	36
Factor VII (stable)	Liver	3–6
Factor VIII (AHF-A)	Liver, extrahepatic sites	12
Factor IX (Christmas, AHF-B)	Liver	24
Factor X (Stuart-Prower)	Liver	40
Factor XI	Liver	80
Factor XII (Hageman)	Liver	50
Factor XIII	Liver, extrahepatic sites	120–200
vWf	Endothelium	10–24

Adapted from Bolliger D, Gorlinger K, Tanaka KA and Warner DS. Pathophysiology and treatment of coagulopathy in massive haemorrhage and hemodilution. Anesthesiology 2010;113(5):1205–1219
AHF-A anti-haemophilic factor A, *AHF-B* anti-haemophilic factor B

13.6 Fibrinogen

This acute phase reactant protein is produced in the hepatocytes and consists of six polypeptide chains. High levels of fibrinogen concentration are seen in cholestatic jaundice and hepatocellular carcinoma whereas low fibrinogen concentration is seen as the patient progresses towards end-stage disease [9, 10]. In advanced liver failure, there is reduced level of fibrinogen as well as there is qualitative abnormality leading to dysfibrinogenemia which is functionally abnormal. There is abnormal alpha chain with raised sialic acid content in fibrinogen.

The normal level of fibrinogen in the blood is 2–4 g/L, which makes it the most abundant coagulation factor found in the plasma. A large amount of fibrinogen is engulfed in the formation of stable thrombus. Fibrinogen above 3 g/L is generally considered as adequate for producing haemostasis whereas plasma levels below 1 g/L are considered inadequate. Looking at the influence of fibrinogen correction on transfusion requirement in liver transplant recipients, Roullet et al. found that there was no decrease in blood transfusion related to fibrinogen level in the blood [11]. Fibrinogen given pre-emptively to liver transplant recipients does produce change in the thromboelastographic parameters leading to increase in the maximum amplitude (mA) but these improvements did not translate into a reduction in blood transfusions. In both acute and chronic liver disease, there is qualitative change seen in the fibrinogen with quantitative effect seen only during end-stage liver failure.

13.7 von Willebrand Factor (vWf)

vWf is a high molecular weight protein multimer and an important partner in supporting haemostasis. The importance of vWf lies in the fact that this protein has a high affinity for collagen present on the vessel wall as well as glycoprotein 1b which is present on the platelet surfaces. This factor acts as a combining medium between platelets and the vessel wall where the clot formation takes place. High levels of vWf are seen in patients with chronic liver disease and cirrhosis. The mechanisms responsible for the elevated levels of vWf are possibly due to inflammation or infection and the other reason being reduced clearance of this factor by the liver. vWf levels are substantially increased in acute liver failure where there is other evidence of systemic inflammatory response (SIRS) as well. In chronic liver disease there is formation of nitric oxide due to the underlying portal hypertension. The nitric oxide acts as a stimulus for liberation of vWf from the endothelium. In essence there are increased plasma level of vWf in both acute and chronic liver disease.

The activity of vWf is controlled to an extent by ADAMTS13. In chronic liver disease ADAMTS13 levels are reduced in the plasma thereby promoting procoagulant effect of vWf [12].

13.8 Platelets

Thrombocytopenia is seen in 49–60% of the patients with end-stage liver disease. Generally the platelet count is not below 30,000/cmm and spontaneous bleeding is not seen because of low platelet count. The main cause of thrombocytopenia is due to portal hypertension leading to enlargement of the spleen causing sequestration platelets. Besides there is impaired production of platelets, increased platelet destruction due to immunological reasons. Other causes such as alcohol, disseminated intravascular coagulation, sepsis, folate deficiency and drugs may be responsible for platelet deficiency. A markedly enlarged spleen can sequestrate up to 90% of the total platelet mass [13, 14].

A normal platelet count of 150,000/cmm to 450,000/cmm offers a huge functional reserve which is also observed in the various other biological parameters like haemoglobin, WBC, etc.

Thrombocytopenia of chronic liver disease is partly because of lack of thrombopoietin (TPO) and treatment with TPO agonists leads to increase in platelet count and reduced platelet transfusion and bleeding. This also led to increased incidence of portal vein thrombosis and termination of the clinical study [15, 16].

Platelets play a very important role in clot formation; it helps in clot formation in two stages:

1. **Primary Haemostatic Plug**—Platelets through an interaction with vWf adhere to the damaged vessel wall, thereby leading to aggregation of platelets and formation of primary haemostatic plug. Platelets in the presence of exposed collagen and vWf leads to alteration in the shape of platelets and release of adenosine diphosphate and thromboxane A2, both of which cause the platelets to aggregate.
2. **Thrombin Generation**—In the presence of activated clotting factors platelets support the formation of thrombin leading to stable clot formation. Platelets count up to 60,000/cmm are usually enough to generate this response [17].

In liver disease ADAMTS13 levels are decreased in the plasma. ADAMTS13 normally makes a cleavage in the platelet vWF and thereby promotes clot formation (Fig. 13.4) [12, 18].

Myelosuppression can also contribute to the low platelet count, and this can be seen in hepatitis C virus (HCV infection), other acute viral infections, folic deficiency and chronic alcohol use [19, 20].

A large amount of platelets—up to 90%—are sequestrated in the spleen but splenectomy is generally not indicated in these patients with chronic liver disease. Splenectomy is associated with a risk of secondary portal vein thrombosis which can lead to bleeding from oesophageal varices and a difficult subsequent liver transplant [21]. There are reports of splenic artery embolization with reduction in the splenic blood flow leading to improvement in platelet count [22].

Intrinsic defects in the platelets as well as abnormalities in other plasma factors also add to the hand in cholestatic liver disease there can be hyperactive platelet functioning which can be abnormal functioning of platelets. This can be detected either by platelet function assay (PFA-100) or on the other hand by thromboelastography (TEG) [23]. Thromboelastography is a test of whole blood clotting and measures platelet function which is detected by maximum amplitude (mA) on the graph [24].

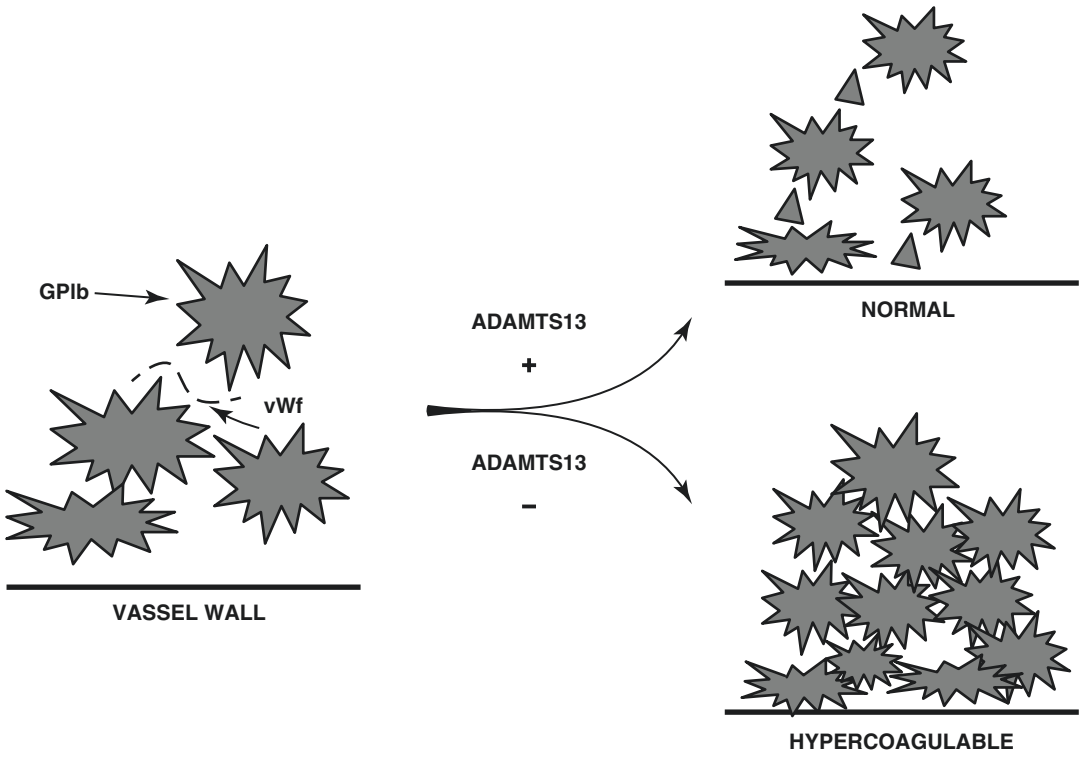


Fig. 13.4 Role of ADAMTS13 in clot formation

13.9 Anticoagulant Factors

1. **Anti-Thrombin III:** This is a glycoprotein which is synthesized by the liver and endothelium and does not require vitamin K for its activation. Anti-thrombin III levels are reduced in liver disease as the synthetic function are affected with the progression of the disease. The levels are also decreased due to its consumption during the process of fibrinolysis seen in end-stage liver disease. There are no preparations of anti-thrombin III available and its replacement is generally not indicated (Table 13.2).
2. **Protein C and Protein S:** These are also glycoproteins which are synthesized mainly by the hepatocytes and are dependent on vitamin K. Disease progression in the liver leads to decline in both protein C and protein S but their levels rarely fall below 20% of the normal (Table 13.2).

Table 13.2 Sites of synthesis of anticoagulant factors

Factors	Synthesis	Half-life (h)
Anti-thrombin II	Liver, extrahepatic sites	48–72
Protein C	Liver, endothelium	10
Protein S	Liver, endothelium	42

Adapted from Bolliger D, Gorlinger K, Tanaka KA and Warner DS. Pathophysiology and treatment of coagulopathy in massive haemorrhage and hemodilution. Anesthesiology 2010;113(5):1205–1219

13.10 Fibrinolytic and Antifibrinolytic System

In advanced liver disease, it is not uncommon to find evidence of fibrinolysis. The laboratory tests revealed elevated level of fibrinogen degradation products, raised level of plasma D-Dimer and shortened whole blood Euglobulin clot lysis time. There are high levels of circulating plasminogen activators due to their decreased clearance in the liver. The increase in tissue

plasminogen activator (tPA) is also accompanied with normal or even elevated levels of tPA inhibitor. Hyperfibrinolysis is not seen in patients with acute liver disease but is seen in up to 31% of patients with compensated cirrhosis [25]. Hyperfibrinolysis is almost universal in patients with uncontrolled ascites. Agarwal S et al. reported an incidence of hyperfibrinolysis in 93% of the patients with ascites [26]. On analysing the ascitic fluid of patients with severe liver disease there was evidence of low fibrinogen, and increased levels of FDPs and D-Dimer. This is evidence of hyperfibrinolytic activity which could be because of absorption of ascitic fluid into the systemic circulation. Hyperfibrinolysis can contribute to increased incidence of bleeding from mucus membranes.

13.11 Disseminated Intravascular Coagulation (DIC)

As the liver disease progresses and reaches the end stage, there is evidence of low-grade disseminated intravascular coagulation (DIC). This coagulation concept involves formation of fibrin deposits and their partial breakdown. There is increase in fibrin degradation products (FDPs) as well as reduction in serum fibrinogen levels. DIC in end-stage liver disease is typically accompanied with prolongation of PT and PT, APTT as well as reduction in the platelet count. As the disease progresses, there is tendency to increase in severity of DIC [27, 28]. The suspicion of DIC in cirrhotic patient is based on worsening of coagulation test results and disproportionate reduction in platelet count. There is generally a triggering clinical event like bleeding or infection. In the presence of DIC there is also reduction of factor VIII as well as factor V.

Central to the development of DIC is activation of thrombin due to high level of tissue factor and consequently activation of extensive coagulation pathway [29]. There is fibrin deposition in small vessels leading to venous and arterial thrombosis which finally affects various organs and may even lead to multi-organ failure. On consumption of various clotting factors as well as activation of DIC there is wide spread bleeding manifestation. Accelerated intravascular coagulation and fibrinolysis (AICF) has been reported in about 30% of the patients with cirrhosis and this is dependent on the severity of the liver disease. This phenomenon is seen more in the portal venous system compared to the arterial system [30]. The trigger for AICF could be endotoxaemia which is evident in the portal circulation, leading to the release of IL6 and TNFα which stimulate intravascular coagulation [31].

13.12 Hypercoagulability

This refers to the propensity of developing an appropriate clot in a patient although bleeding is the more recognized complication of chronic liver disease. Portal vein thrombosis has been reported in up to 26% of patients with cirrhosis [32] and a variable number of patients also develop deep vein thrombosis or pulmonary emboli. The risk of portal vein thrombosis increases with the severity of liver disease and increased mortality in those who undergo orthotopic liver transplant (OLT) [33].

There is an increase in vWf in chronic liver disease and this remains elevated for up to 10 days after OLT. The activity of vWf is further enhanced due to a lack of ADAMTS13 which results in the stability of platelets in circulation.

Hypercoagulability can lead to Hepatic Artery Thrombosis (HAT) post-operatively in OLT. There is an increased risk of HAT in patients who have familial amyloidotic polyneuropathy and acute intermittent porphyria. Similarly cytomegalovirus (CMV) is also known to increase the risk of developing HAT [34]. The risk of HAT is significantly reduced in these patients by treatment with aspirin.

The incidence of deep vein thrombosis can be minimized by use of Low Molecular Weight Heparin (LMWH) but this has to be weighed against the risk of bleeding post-operatively. The monitoring of LMWH is difficult as anti-Xa testing in the laboratory is not freely available. This therapy works both for DVT prophylaxis and for preventing HAT.

13.13 Assessment and Correction of Coagulation Status Before Invasive Procedures

1. **Paracentesis:** There may not be any signs of bleeding in advanced liver disease if there is not intervention. Minor intervention can trigger the bleeding process in patients with end-stage liver disease and may have serious or even life-threatening consequences. Ascites is a common manifestation in ESLD which may or may not respond to conservative management of diet and diuretic. Such refractory ascites requires paracentesis. Some patients may end up having serial therapeutic paracentesis requiring drainage every 2 weeks. Haemoperitoneum and damage to the intestine during needle insertion are potential serious complication of paracentesis. Up to 3% of patients undergoing paracentesis may develop excessive bleeding to haemoperitoneum and some of them even require transfusion. Severe coagulation defects (INR > 1.5 and Platelets <50,000/cmm) may require transfusion of FFP and platelets respectively. In presence of portal hypertension there are multiple porto-systemic shunts, some of which could be seen in the anterior abdominal wall. Ultrasound-guided paracentesis can minimize these complications in most of the patients with refractory ascites. Large volume paracentesis normally requires supplementation of albumin—8 g/L or fluid removed to maintain the haemodynamic stability [35]. Paracentesis normally would not require any support of coagulation unless the platelet count is <30,000/cmm or INR is >2.5. Carefully selected needle placement for paracentesis, avoiding inferior epigastric artery and the porto-systemic shunt, enables a safe therapeutic intervention (Fig. 13.5). To support this, there is a large study of 11,000 patients where no haemorrhagic complication was seen in patients with platelet counts as low as 19,000/cmm and INR upto 8.7 [36].
2. **Liver Biopsy:** It is not uncommon to do a liver biopsy to establish the diagnosis of advancing liver disease. There is always a hazard of developing intra-peritoneal bleeding in the process of doing liver biopsy. Earlier bleeding time was used as a reference to know the suitability to do this procedure but has become an obsolete investigation. Platelet count is a value which is relied upon and a value above 60,000–80,000/cmm is considered safe [37]. Another parameter used to assess the coagulation status is prothrombin time (PT). Prolonged PT > 4–6 s is considered abnormal with likelihood of bleeding after the procedure. One study coated International Normalize Ratio (INR) > 1.5 as a risk factor for post-procedure bleeding [38]. There are other options to minimize the risk of bleeding following liver biopsy. A transjugular biopsy or a plugged biopsy can be used to minimize the risk of bleeding [39]. Most centres have their own cut-off values for performing a liver biopsy, one of the UK guidelines requires platelet count above 80,000/cmm and a survey from Mayo Clinic suggested a count of >50,000/cmm [40].
3. **Central Venous Access:** Accessing the central vein has a potential of forming haematoma or even intrathoracic collection of blood—haemothorax. The preferred site to avoid these complications would be access through internal jugular vein. In this era of ultrasound central vascular access has become

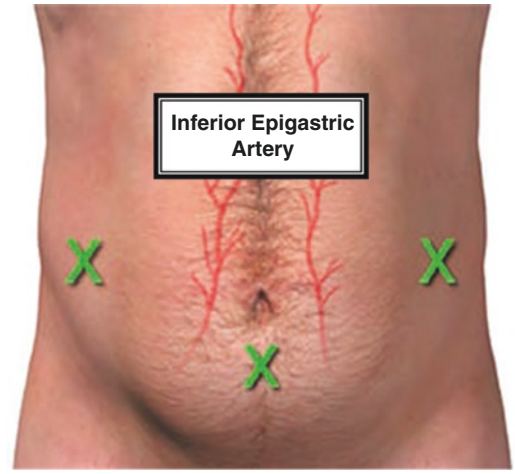


Fig. 13.5 Safe sites of paracentesis avoiding inferior epigastric artery

less traumatic with minimal bleeding complication (Fig. 13.6). Reported major bleeding complications in patients with end-stage liver disease are in the range 0–0.2%. It is therefore not necessary to administer blood products before obtaining central venous access, especially if it is done under the ultrasound guidance [41, 42].

4. **Coronary Angiography:** Up to 28% of patients over the age of 50 years may have coronary artery disease in patients with CLD [43, 44]. Patients with risk factors for CAD, aetiology of NASH and those with non-coronary artery disease may need to undergo coronary artery angiography before liver transplantation. Performing coronary angiography can lead to haematoma formation, pseudoaneurysm as well as increased bleeding from the puncture site in a coagulopathic liver transplant recipient. Bleeding issue can be minimized for this investigative procedure of coronary angiography by using radial artery route instead of the traditional femoral artery (Fig. 13.7). One drawback of this procedure is also because of the use of contrast used in angiography. Renal function can be compromised and may lead to overt renal failure in susceptible individuals. The measures taken

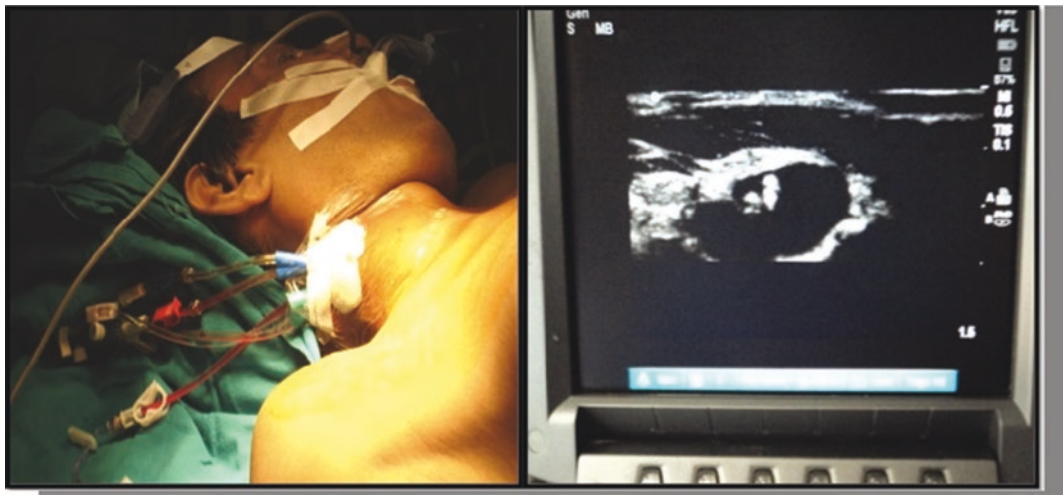


Fig. 13.6 Ultrasound-guided central venous access

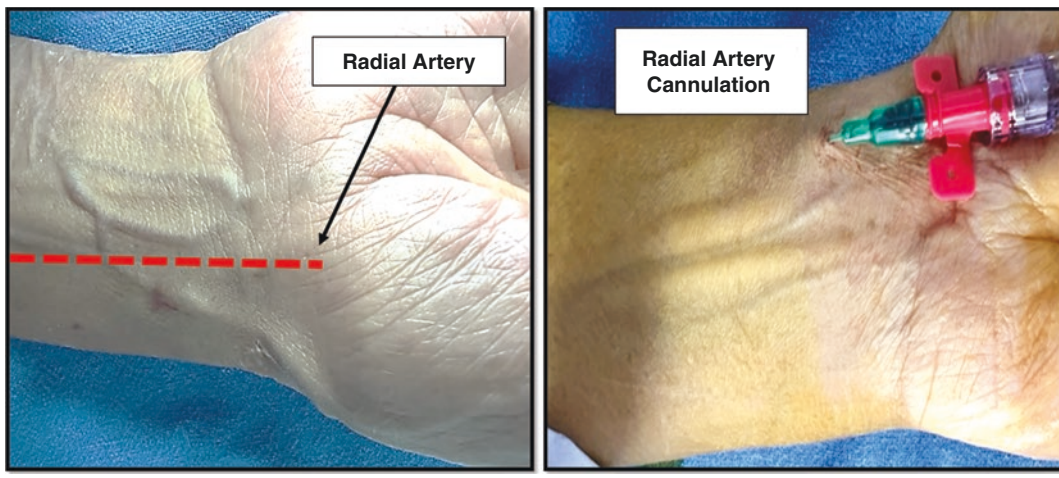


Fig. 13.7 Percutaneous radial artery cannulation

to offset development of renal compromise can be in the form of adequate hydration as well as use of free radical scavenger *N*-acetylcysteine given prophylactically.

13.14 Coagulation and Infection

Infection has been reported in cirrhotic patients which can lead to complication of bleeding. Sepsis is known to result in bleeding from oesophageal varices resultant from portal hypertension. Infection produced by the bacteria leads to production of endotoxin which produces tissue factors expression on macrophages and activation of clotting and fibrinolytic mechanism. Infection in advanced liver disease leads to production of cytokines—interleukin-1 (IL1), IL6 and tumour necrosis factor (TNF). These cytokines are precursor to fibrinolysis and can also activate clotting by stimulating the extrinsic coagulation pathway [45]. Generally a hypocoagulable state evolves in cirrhotic patients with sepsis which can manifest as bleeding from oesophageal varices [46].

13.15 Portal Hypertension and Bleeding

The risk of bleeding in end-stage liver disease is either because of a procedure being carried out or this can happen spontaneously due to the presence of portal hypertension. The patients with cirrhosis are not spontaneously anticoagulated but are in a state of rebalanced haemostasis. In a patient with oesophageal varices, reduction of portal pressures leads to control of bleeding. Institution of Transjugular Intrahepatic Portosystemic Shunt (TIPS) in patients with high HVPG gradient results in control of active bleeding. In the presence of high portal pressure there is no evidence to control bleeding with fresh frozen plasma or platelet transfusion. These interventions have the potential of increasing the risk of acute lung injury as well as further increasing the portal pressures. Other methods to control bleeding is use of non-selective beta-blockers, endoscopic ligation of varices, prophylactic desmopressin, anti-fibrinolytic agents or recombinant factor VIIa [47, 48].

13.16 Conclusion

Chronic and acute liver disease is frequently accompanied with changes in the coagulation parameters which can cause concern. There is an imbalance of haemostatic factors—pro- and anti-haemostatic—with a rebalance created at a different level which makes them prone to bleeding as well as hypercoagulable state. Conventional routine laboratory tests are not able to identify patients at risk. Point of care testing like TEG has the potential to identify the coagulation abnormalities. Still a lot of work needs to be done to validate the results of viscoelastic test in predicting bleeding or thrombosis. Prophylactic transfusion of blood product before any procedure needs to be guided by viscoelastic test. There is a strong recognition of thrombotic complications in patients with liver disease and the need to use necessary anti-thrombotic therapy.

Key Points

- Liver disease can result in both bleeding and thrombotic complications.
- Conventional tests of coagulation—PT/APTT—do not predict risk of thrombosis or bleeding.
- There is a delicate balance between pro- and anticoagulant in liver disease.
- Portal hypertension is more of a culprit in bleeding patients.
- Liver disease patients do not always require correction of coagulation parameters.
- Diagnostic/therapeutic procedures like paracentesis and coronary angiography do not always require correction of coagulation.
- Surgical intervention can upset the rebalanced haemostasis.
- Acute liver failure may exhibit hypercoagulable state in spite of normal PT.

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